Base catalyzed reaction of ethylthioglycolate with β-aryl-β-(methylthio) acroleins: A general method for the synthesis of 2-carbethoxy-5-substituted/4, 5-annulated thiophenes in high overall yields

G. Byre Gowda, C.S. Pradeepa kumara, N. Ramesh, M.P. Sadashiva, H. Junjappa

PII: S0040-4039(16)30054-5
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.01.055
Reference: TETL 47219

To appear in: *Tetrahedron Letters*

Received Date: 30 November 2015
Revised Date: 14 January 2016
Accepted Date: 17 January 2016

Please cite this article as: Byre Gowda, G., Pradeepa kumara, C.S., Ramesh, N., Sadashiva, M.P., Junjappa, H., Base catalyzed reaction of ethylthioglycolate with β-aryl-β-(methylthio) acroleins: A general method for the synthesis of 2-carbethoxy-5-substituted/4, 5-annulated thiophenes in high overall yields, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.01.055

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Base catalyzed reaction of ethylthioglycolate with β-aryl-β-(methylthio) acroleins: A general method for the synthesis of 2-carbethoxy-5-substituted/4, 5-annulated thiophenes in high overall yields.

G. Byre Gowda [a, b], C. S. Pradeepa kumara [a, b], N. Ramesh[b], M. P. Sadashiva [a,]*, H. Junjappa [b,]*

[a] *Department of Studies in Chemistry, University of Mysore, Mysuru 570 006, India*
[b] *Department of Chemistry, REVA Institute of Science and Management, Yelahanka,, Bengaluru 560 064, India*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Ethyl thioglycolate
Annulated thiophene
Methylthio
Chloroacroleins
carbethoxy

ABSTRACT

(Methylthio)acroleins 1a-m were shown to be stable unlike their counterpart the chloroacroleins and their efficacy as 1,3-dielectrophilic properties have now been examined successfully in this work. They are shown to react with ethyl thioglycolate in the presence of anhydrous potassium carbonate in boiling ethanol to yield the corresponding 5-substituted / 4,5-annulated-2-carbethoxy thiophenes in 70-80% overall high yields.

.

Ever since Arnold and Zemlicka[1] extended the then known Vilsmeir-Haack[2] formylation reaction to active methylene carbonyl compounds they found that the course of reaction yielded the corresponding *β*-chloroacroleins instead of only the corresponding aldehydes in moderate to good yields. These chloroacroleins have been proved to be powerful 1, 3-dielectrophilic building blocks and employed extensively for the synthesis of five and six member heterocycles, resulting in an extensive literature on these developments in several reviews[3,4,5,6]

However, the chemistry of these chloroacroleins suffers certain limitations due to their unstable nature. Hence many workers generally prefer to synthesize them freshly and use immediately in the following steps. In some studies attempts have been made to develop stabilizers to prolong the life of these intermediates. For example Paquette and co-workers[7] have suggested that a small quantity of anhydrous sodium acetate could prolong the life of chloroacroleins derived from cyclohexanone for two weeks without apparent decomposition.

Since the chemistry of *β*-(methylthio)acroleins and the corresponding chloroacroleins are similar to that of α-oxoketene dithioacetals in terms of their structural similarity and common behavior towards 1,2- and 1,3 bi-nucleophiles to yield the corresponding five and six member heterocycles[8], the vast body of literature on *β*-chloroacroleins therefore assumes greater synthetic potential as 1, 3-dielectrophilic three carbon building blocks. However, they are not available commercially for their general use as synthetic intermediates due to their instability. The identity of these intermediates with α-oxoketene dithioacetals prompted us to examine the possible structural change without disturbing their 1, 3-dielectrophilic centers, so that we have a large body of stable building blocks at hand to explore their chemistry. Our experience in organosulfur chemistry prompted us to transform the active chlorine group to the corresponding methylthio group so that the new class of building blocks thus obtained may display improved stability without sacrificing their 1,3-dielectrophilic character. There are couple of methods to achieve the displacement of active chlorine in organic molecules: Since the methanethiol itself is a gas available only in cylinders, which is difficult to avail in many laboratory facilities, there are other sources of methyl mercaptans such as methylthiolesters,[9] and methylthiouraniumsulphate[10] which can produce sodium methylate under alkaline hydrolytic conditions.

Interestingly, recently Degani and co-workers[11] have found that Dimethyldithiocarbonate (DDC) is an excellent source of methylmercaptan which can be generated *'insitu'* in the presence of 30% potassium hydroxide. We have successfully shown that the active chlorine in chloroacroleins could be easily displaced by Degani's method as described in our earlier publication[12].

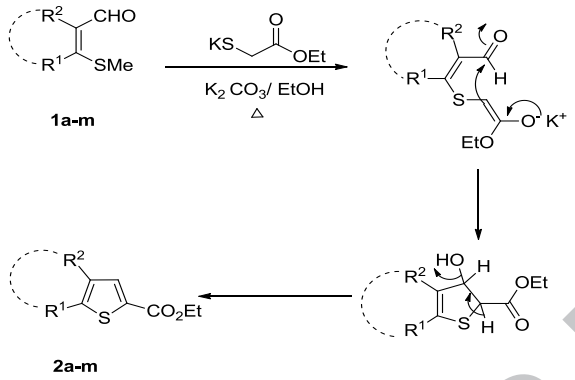
* Corresponding author. Tel.: +91 98453 72078

Email address: junjappa_123@rediffmail.com; mpsadashiva@gmail.com

We became further interested to examine their synthetic applications on the lines of the corresponding chloroacroleins and oxoketene dithioactals.

We here in report our first example of synthetic application involving the reaction of (methylthio)acroleins with ethylthioglycolate in the presence of base with a view to develop a method for the synthesis of corresponding 2-carbethoxy-5-substituted thiophenes[25]. Thus when a solution of equimolar quantities of (methylthio)acroleins **1a** and ethylthioglycolate dissolved in ethanol was refluxed in the presence of anhydrous potassium carbonate afforded the corresponding 2-carbethoxy -5- substituted thiophene **2a** in 81% yield (Scheme 1)

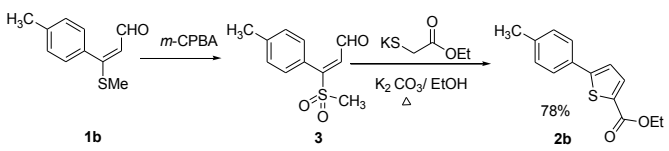
This is our first attempt to verify the reactivity of β-(methylthio) acroleins with ethylthioglycolate and results were presented here in comparison to that of their precursors haloacroleins.



Scheme 1

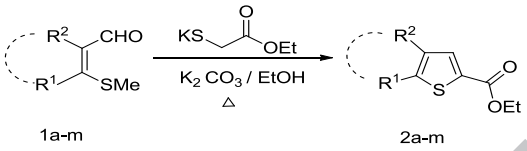
However it must be noted that this thiophene was reported earlier by Mavrova and co-workers[13] by reaction between phenyl chloroacrolein and ethylthio glycolate in the presence of base to yield the corresponding thiophene **2a** in 40% yield. Also Reddy and co-workers have reported the synthesis of **2a** under microwave conditions using phenyl chloroacrolein in the presence of base and obtained slightly improved yield of 62%. They have also carried out this reaction under conventional reaction conditions and have not reported the yields separately.

Mavrova and coworkers[13] have also reported the synthesis of thiophene **2b** by reacting *p*-tolyl chloroacroleins **1b** in the presence of pyridine to yield the corresponding thiophene **2b** in 56% yield. We have obtained the same thiophene **2b** by reacting the corresponding *p*-tolyl-(methylthio) acrolein **1b** with ethylthioglycolate as described above to yield the corresponding thiophene in 78% yield. The same thiophene **2b** was also prepared by us by treating *p*-tolyl (methylthio) sulphone acrolein **3** (Scheme 2) with ethylthioglycolate in the presence of potassium carbonate in boiling ethanol to an improved yield of



Scheme 2

Table-1: Synthesis of 2-carbethoxy-5-substituted/4, 5-annulated thiophenes (Scheme 1)



Entry	R^1	R^2	Product	Mp (°C)	Yield (%)
1	C_6H_5	H	**2a**	Liq	81
2	C_6H_4-*p*-Me	H	**2b**	80-81	78
3	C_6H_4-*p*-OMe	H	**2c**	72-76	79
4	C_6H_4-*p*-F	H	**2d**	73-77	78
5	C_6H_4-*p*-Cl	H	**2e**	79-83	76
6	C_6H_4-*p*-Br	H	**2f**	77-81	80
7	C_6H_4-*m*-NO_2	H	**2g**	79-82	84
8		H	**2h**	liq	79
9	C_6H_5	CH_3	**2i**	liq	72
10			**2j**	liq	79
11			**2k**	liq	80
12			**2l**	80-84	76
13			**2m**	124-128	71

Reaction conditions[25]: A mixture of (methylthio) acrolein (2.07 mmol) and ethyl thioglycolate (2.07 mmol) in ethanol (10 mL) was heated to 80 ^{0}C for 1h (monitored by TLC)

85%. The required sulphone **3** was obtained by oxidation of (methylthio) acrolein **1b** by m-Chloroperbenzoic acid (*m*-CPBA) in 60% yield[26]. However the average yield of **2b** through sulphone is 72.5% involving two steps which is less than the yield directly from the corresponding (methylthio) acroleins **2a**. Therefore it was decided to continue the remaining reactions directly from (methylthio) acroleins.

In the next series of experiments (methylthio)acroleins **1c, 1d, 1e** and **1f** (Table 1) were reacted with ethylthioglycolate under the described reaction conditions to yield the corresponding thiophenes **2c, 2d, 2e** and **2f** in 76-80% yields (Table 1)

Interestingly Reddy and co workers[14] and others[15,16] have reported the synthesis of these thiophenes in comparatively low yields both by microwave and conventional methods. We therefore consider our yields from (methylthio) acroleins are much higher than corresponding chloroacroleins. It must be however noted that low yields obtained by earlier two research groups attributed to their slow decompositions of the chloroacroleins during the course of the reaction with ethylthioglycolate.

We further examined the thiophenation from (methylthio) acroleins **1h-m** (Table 1) to yield the hitherto unknown thiophenes **2h-2m** respectively. The **(**methylthio) acrolein **1g** yielded the corresponding thiophene **2g** in 84% yield. Similarly the (methylthio) acrolein **1h** derived from 2-acetylthiophene reacted with ethylthioglycolate under the described reaction conditions to yield the corresponding 2-carbethoxy-5-(2-thienyl)-thiophene **2h** in 79% yield. The other (methylthio) acrolein **1i** derived from propiophenone reacted with ethylthioglycolate under identical reaction conditions to yield the corresponding 4-methyl-5-phenyl-2-carbethoxy thiophene **2i** in 72% yield. Also the (methylthio) acroleins **1j** and **1k** derived from cyclohexanone and cycloheptanone respectively reacted with ethylthioglycolate under similar reaction conditions to yield the corresponding 4, 5-cycloannulated thiophenes **2j** and **2k** in 79 and 80% yields respectively. Next the (methylthio) acrolein derived from tetralone **1l** also yielded the corresponding 4, 5-annualated -2-carbethoxy thiophene **2l** in 76% yield. Finally the (methylthio)acrolein **1m** derived from 1-phenyl-3-methyl-pyrazoline-5-one similarly reacted with ethylthio glycolate to yield the corresponding pyrazolo-thiophene **2m** in 71% yield.

The mechanism governing this transformation is depicted in Scheme 1. The potassium thioglycolate attacks **1** to displace methylthio group followed by intramolecular attack by enolate carbanian to the aldehyde carbonyl group with elimination of water to yield the desired thiophene (Table 1).

It is therefore interesting to note that the reactivities of both *β*-chloroacroleins and β-methyl thioacroleins displayed identical reactivity with a clear difference of consistently higher yields in the case methyl thioacroleins.

Thiophenes are important class of heterocycles generally used as[17-24] pharmaceuticals and in the area of material science as organic conductors, semiconductors and light emiting diodes etc.,

In conclusion, we have demonstrated that the *β*-(methylthio) acroleins developed by our group display identical 1,3-dielectrophilic reactivity similar to their precursors chloroacroleins with the advantage of better yields of product thiophenes. Therefore the chemistry of this group of building blocks provides greater advantages over the counterpart chloroacroleins in-terms of their stability and yields of the products.

We will continue to explore these new synthetic applications to further confirm their superiority as 1,3-dielectrophilic building blocks.

Acknowledgments

H.J. is grateful to Indian National Science Academy (INSA) for the award of Sr. Scientist. We gratefully acknowledge the CSIR, New Delhi (02(0106)/12 EMR-II Dated 01/11/12) for the financial support through the project. We thank J.N. Moorthy of IIT Kanpur for helping in getting spectral analysis. The authors thank Dr. P Shyamaraju, Chairman, REVA Institute of science and Management, Yelahanka, Bengaluru-560 064.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at:

References and notes

1. Arnold, Z.; Zemlicka, J. *Proc. Chem. Soc.* London. **1958**, 227-251.
2. Vilsmeier, A.; Haack, A. *Ber. Dtsch.Chem. Ges*. **1927,** 60B, 119-127.
3. Masson, C.M *Tetrahedron*. **1992,** 48, 3659-3726.
4. Jones, G.; Stanforth, S.P. *Organic reactions*, In: Larry E.Overman et.al., John Wiley and Son's, **2004**, 56, 355-659.
5. Brahma, S.; Ray, J.K. *Tetrahedron*. **2008,** 64, 2883-2896.
6. Rajput, A. P.; Girase, P. D. *Int.J.Pharm.Chem.Biol. Sci.* **1913,** 3, 25-43.
7. Paquette, L.A.; Johnson, B.A.; Hinga, F.M. *Org. Syn. Coll. Vol.* **1973**, V, 215-217.
8. Junjappa, H.; Ila, H.; Asokan, C.V. *Tetrahedron*. **1990**, 46(16) 5423-5506.
9. Frejd,T.; karlsson, J. O.; Gronowitz,S. *J. Org..Chem.* **1981**, 3132-3135.
10. Windus,W; Shildneck,P.R. *Org. Syth.* **1934**, 14, 54.
11. Degani , I.; Fochi,R.; Regondi,V. *Synthesis*. **1983**, 630-632.
12. Byre Gowda, G.; Charanraj ,T.P.;Pradeepakumara , C.S.; Ramesh, N.;Thomas, S.P.; Sadashiva, M.P.; and Junjappa,H, *Tetrahedron Lett.* **2014**, 55, 4475-4479.
13. Mavrova A.T.; Wesselinova, D.; Tsenov, Y.A.; and Denkova. P. *Eur. J. Med. Chem.* **2009**, 44, 63-69.
14. Reddy G.J Latha, D.; Sailaja,S.;Pallavi K.; Srinivas Rao, K. *Heterocycl. Commun.* **2004**, 10 (6) 411-414.
15. Hauptmann, S.; Weibenfels, M.; Scholz, Werner, E. M.; Kohler, J Weisflog, J. *Tetrahedron Lett*. **1968,** 11, 1317-1319.
16. Fusco, R.; Sannicolo, F. *J. Org. Chem*. **1982,** 47, 1691-1696.
17. Holmes, J.M.; Lee G.C.M.; Wijono M.; Weinkam, R.; Wheeler, L.A.; Garst. M.E.; *J. Med. Chem*. **1994**, 37, 1646-1651.
18. Luker, T. J.; Beaton H.G.; Whiting, M.; Mete, A.; Cheshire, D.R *Tetrahedron Lett*. **2000**, 41, 7731-7735.

19. Pinto, I.L.; Jarvest, R.L.; Serafinowska, H.T.; *Tetrahedron Lett.* **2000**, 41 1597-1600.
20. Kiani, M.S.; Mitchell, G.R.; *Synth.Met.* **1992,** 46, 293-306.
21. Wolf, J. J.; Wortmann.R. Adv. *Phy.Org. Chem*. **1999**, 32, 121-217.
22. Morrison , J.J.; Murray, M.M.; Li. X.C.; Holmes, A, B.; Moratti; S.C.; Friend, R.H.; Sirringhaus, H. *Synth. Met*. **1999**, 102,987.
23. Li, X.C. Sirringhaus, H.; Garnier, F.; Holmes, A, B.; Moratti. S.C.; Feeder, N.; Clegg. W.; Teat, S.J.; Friend, R.H. *J. Am. Chem. Soc.* **1998**, 120, 2206-2207.
24. Greenham, N.C.; Moratti, S.C.; Bradley, D.D.C.; Friend, R. H.; Holmes, A. B. N.; *Nature* (London) 1993, 365, 628.
25. General procedure for the preparation of 2-carbethoxy-5-substituted/4, 5-annulated thiophenes (2a-2m):
To a solution of *β*-(methylthio) acrolein (0.44g 2.07 mmol) in ethanol 10 mL was added ethyl thioglycolate (0.249g 2.07 mmol) and anhydrous potassium carbonate (0.28g, 2.07 mmol) at room temperature. The mixture was heated to reflux for one hour (monitored by TLC), cooled to room temperature and evaporated the solvent. The residue was added water and extracted with ethyl acetate. The combined extracts were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give crude thiophene which was purified by column chromatography over silica gel using ethyl acetate-petroleum ether (5:95) as eluents.
26. Procedure for the preparation of sulfone derivative **2b**: To a solution of *β*-(methylthio) acrolein (0.178g 0.001mol) in dichloromethane (10 mL) was added *m*-CPBA at room temperature. The reaction mixture was stirred at room temperature for 3h. The progress of the reaction was monitored by TLC (20% ethyl acetate: hexane). The reaction mixture was quenched with saturated sodium sulphite (monitored the quenching process by using 10% potassium iodide solution). Separated the organic layer and given wash with saturated sodium bicarbonate solution. The organic layer was dried over anhydrous sodium sulphate and evaporated the solvent under reduced pressure to give sulphone derivative. The crude product as such used in the next step without purification.

Graphical Abstract

Base catalyzed reaction of (ethylthio) glycolate with β-(methylthio) acroleins: A general method for the synthesis of 2-carbethoxy-5-substituted/4, 5-annulated thiophenes in high overall yields.

Leave this area blank for abstract info.

G. Byre Gowda [a,b], C. S. Pradeepa kumara [a,b], N. Ramesh[b], M. P. Sadashiva [a,]*, H. Junjappa [b,]*